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The effect of sympathomimetic epinephrine (10 ug/kg, i.v.), beta-adrenergic antagonist propranolol (0.2 mg/kg, i.v.) and alpha-adrenergic antagonist phenoxybenzamine (1 mg/kg, i.v.) on maximal exercise in normal sheep was investigated. Maximal exercise in control sheep showed a mean maximum oxygen consumption (VO_2) of 47.6 ± 6.7 ml O_2/min/kg. Maximum VO_2 after pretreatment with epinephrine, 51.6 ± 8.7 ml O_2/min/kg, was not significantly different from control. Maximum VO_2 after pretreatment with propranolol and phenoxybenzamine, 35.4 ± 15.3 and 40.8 ± 8.2 ml O_2/min/kg, respectively, were both significantly less than control ($p<.05$). The anaerobic threshold (AT) was unaffected by either epinephrine, propranolol or phenoxybenzamine. Maximum exercise in sheep caused a mean 42% increase in hematocrit and 44% increase in hemoglobin. This exercise-induced hemoconcentration was unaffected by propranolol but was partially blocked by phenoxybenzamine. Maximal exercise in sheep caused significant decreases in bicarbonate and pH and significant increases in jugular venous P_{O_2} and O_2 content. Increases in O_2 content from rest to maximal exercise, 7.6 ± 1.3 to 12.7 ± 1.8 g/100ml ($p<.05$), were less when sheep were exercised after pretreatment with phenoxybenzamine, 7.9 ± 1.2 to 10.8 ± 0.7 g/100ml ($p<.05$).

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Effects of Epinephrine, Phenoxybenzamine, and Propranolol on Maximal Exercise in Sheep

Thomas G. Mundie, Adolph J. Januszkiewicz, and Gary R. Ripple

Abstract | The mixed adrenergic agonist, epinephrine (10 μg/kg, i.v.), the ß-adrenergic receptor antagonist, propranolol (0.2 mg/kg, i.v.), or the α-adrenergic receptor antagonist, phenoxybenzamine (1 mg/kg, i.v.), were administered to sheep immediately before maximal incremental exercise. The effects of each of these drugs on hemoglobin (Hb) concentration during maximal exercise and on maximal exercise performance were investigated. The maximal incremental exercise protocol began at 4.0 km/h and 0% grade and finished at 5.6 km/h and 12% grade, with speed or grade increases every 1.5 minutes. Maximal exercise in control (untreated) sheep caused a mean 42% increase in hematocrit and 44% increase in Hb. This exercise-induced increase in Hb was unaffected by propranolol but was partially blocked by phenoxybenzamine. Epinephrine caused an immediate increase in Hb which abated during the early minutes of exercise and then subsequently increased toward the end of the exercise challenge. Maximum oxygen consumption ($\dot{V}o_2$) in control sheep was 47.6 ± 6.7 ml/min per kilogram. Maximum $\dot{V}o_2$ after epinephrine, 51.6 ± 8.7 ml/min per kilogram, was not significantly different from control. Maximum $\dot{V}o_2$ after propranolol and phenoxybenzamine, 35.4 ± 15.3 and 40.8 ± 8.2 ml/min per kilogram, respectively, were both significantly less than control exercise ($P < 0.05$).

It is known that about 25% of the total red blood cell volume of sheep is stored in the spleen in a highly concentrated form (1). Contraction of the spleen due to excitation, submaximal exercise, or intravenous epinephrine results in an increase in hematocrit (HCT) and hemoglobin (Hb) (2, 3). Moreover, bolus intravenous epinephrine induces temporal splenic concentration with a maximal effect within 15 seconds (3). Catecholamines released during exercise induce cardiovascular and metabolic adjustments necessary to meet the body's increased metabolic demands induced by exercise. Catecholamines increase heart rate, ventilation, and pulmonary arterial oxygen saturation (4, 5), while stimulating glycolysis, lipolysis, and gluconeogenesis (6). Heavy-to-intense exercise causes significant increases in plasma levels of epinephrine and norepinephrine (7). Circulating catecholamines are known to increase with time as exercise progresses toward exhaustion (8). Endurance training results in a decrease in catecholamine release at the same level of exercise (7).

The role of catecholamines in exercise physiology has been elucidated by studies of the effects of α- and ß-adrenergic receptor antagonists during exercise. Beta-blocking agents have been shown to reduce the capacity to perform maximal and submaximal exercise (9). The reduction in exercise capacity during maximal exercise appears to result from diminished cardiac output subsequent to a reduced heart rate (10), while reduction in submaximal exercise capacity appears to be caused by metabolic changes (9). There have been few studies of the effects of α-adrenergic blockade on maximal or submaximal exercise performance (11, 12) and its effects remain unclear.

We investigated the effects of exogenous epinephrine, a mixed adrenergic agonist; phenoxybenzamine, an α-adrenergic receptor antagonist; and propranolol, a ß-adrenergic receptor antagonist, on Hb concentration and exercise performance during maximal incremental exercise.

Materials and Methods

Animals: Six female sheep (40 to 50 kg) were used in the study. All sheep were closely sheared to avoid overheating during exercise. Before exercise the sheep were fasted for 24 hours but were allowed free access to water. On the day of experimentation, sheep were surgically prepared with a jugular venous catheter, aseptically and under local anesthesia. Catheters were removed after the experiment was completed.

Data acquisition and analysis: A treadmill (model R-3, Pacer Industries, New Carrolton, TX) was modified by constructing a metal retaining cage and vertical padded bars for head restraint. A canine anesthesia mask was modified with a 4 cm i.d. connector to minimize resistance to ventilation. The mask was held on the animal with a muzzle. The sheep were allowed to stand at rest on the treadmill for 3 to 5 minutes before exercise to determine resting ventilatory parameters. A large two-way nonrebreathing valve (model 2700, Hans Rudolf Inc., Kansas City, KS) maintained one-way air flow for inspired and expired air. Expired air was directed to a 15-liter mixing box by 4 cm i.d. corrugated tubing. A large

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low-resistance, heated pneumotachometer (model 3813, Hans Rudolf Inc., Kansas City, KS) and a differential pressure transducer (model MP45-1-871, Validyne Engineering Corp., Northridge, CA) were used to measure air flow exiting the mixing box. The flow signal was integrated to determine volume. The temperature of the air entering the pneumotachometer was measured with a thermocouple (Sensortek, Clifton, NJ). Temperature fluctuations and daily barometric pressure readings were used to correct flow and volume measurements to standard temperature pressure dry (STPD). Mixed expired O_2 (F_EO_2) and CO_2 (F_ECO_2) were measured through a drying tube port in the mixing box using O_2 and CO_2 analyzers (models S-3A/1 and CD-3A, Ametek, Pittsburgh, PA).

Data acquisition was accomplished by using a PC-based data acquisition system. Output voltages for volume, temperature, O_2 and CO_2 were digitized using an A/D board (DT2801, Data Translation Inc., Marborough, MA) and acquired with an 80286-based processor computer (Generation V, Silver Spring, MD). A custom software program was developed using an Asyst® software package (version 2.0, Asyst Software Technologies, Inc., Rochester, NY). The program was written to collect data in 10-second segments without interruption. The computer acquired F_EO_2, F_ECO_2, volume and temperature data and directly transferred them into a software worksheet (LOTUS 1-2-3®, Lotus Development Corp., Cambridge, MA) every 10 seconds. From these values expired minute ventilation ($\dot{V}_E$), *oxygen consumption* ($\dot{V}o_2$), carbon dioxide production ($\dot{V}co_2$), and gas exchange ratio (R) were calculated.

Drug administration: Epinephrine (American Reagent Laboratories Inc., Shirley, NY) and propranolol (Inderol®, Ayerst Laboratories Inc., New York, NY) were purchased from the sources indicated. Phenoxybenzamine was kindly provided by SmithKline Chemicals (Conshohocken, NY).

The drugs were administered on separate days with at least 2 days between experiments. Epinephrine (10 μg/kg, i.v.) was given 2 to 3 minutes before exercise. Dooley *et al.* (3) showed that this dose induces prominent splenic contraction and increased Hb in sheep. On a separate day, epinephrine, at the same dose, was given without subsequent exercise. Propranolol (0.2 mg/kg, i.v.) was given during a 5-minute period immediately before exercise. Phenoxybenzamine (1 mg/kg, i.v.) was diluted to a 50-milliliter volume with physiologic saline. One hour before exercise, phenoxybenzamine was administered intravenously for 15 minutes. Ahmed *et al.* (13) showed that these doses of phenoxybenzamine and propranolol produce adrenergic receptor antagonist effects in sheep.

Treadmill testing: All sheep initially underwent an 8-week training period which included exercise for 20 minutes at 4.0 to 5.4 km/h and 0% grade, twice per day, two or three times a week. The maximal incremental exercise challenge protocol was 13.5 minutes long and incrementally increased speed or grade every 1.5 minutes. The increments consisted of the following: 4.0 km/h, 0% grade; 4.0 km/h, 2%; 4.0 km/h, 4%; 4.0 km/h, 6%; 4.0 km/h, 8%; 4.0 km/h, 10%; 4.8 km/h, 10%; 5.4 km/h, 10%; 5.4 km/h, 12%. Maximal exercise was performed in control sheep and in sheep pretreated with epinephrine, propranolol, and phenoxybenzamine. Control and post-drug treatment maximal exercise challenges were performed randomly to avoid the effects of additional training.

Data analysis: O_2 consumption ($\dot{V}o_2$) and CO_2 production ($\dot{V}co_2$) were calculated using the following equations:

$$\dot{V}o_2\ (ml(STPD)/min/kg) = (\dot{V}_E\ (STPD) * (F_{I}o_2 - F_{E}o_2))/\text{body weight}$$

$$\dot{V}co_2\ (ml(STPD)/min/kg) = (\dot{V}_E\ (STPD) * (F_{E}co_2 - F_{I}co_2))/\text{body weight}$$

Expired minute ventilation was corrected to STPD using measured barometric pressure, air temperature at the pneumotachometer and water vapor pressure, calculated by assuming air saturated at the temperature of the pneumotachometer.

The maximum $\dot{V}o_2$ was defined either as the plateau of $\dot{V}o_2$, despite increasing work intensity, or as the level of $\dot{V}o_2$ at exhaustion. The mean maximum $\dot{V}o_2$ for each condition was determined by averaging the evaluations of the individual $\dot{V}o_2$ profiles which were graded by individuals who had no prior knowledge of the experimental groups.

Differences among repeated samples, as well as differences among treatment groups, were analyzed by an analysis of variance for general linear model and a Duncan's Multiple Range test to determine where significant differences existed at an $\alpha < 0.05$ confidence level. Maximum $\dot{V}o_2$ data for individual animals in the treatment groups were each compared to data from the control group using a paired t test. Data, unless otherwise stated, are expressed as the mean ± standard deviation.

Blood analysis: One milliliter of jugular venous blood was collected every 1.5 minutes during exercise. In addition, two pre-exercise blood samples, 1 to 3 minutes before exercise and immediately before exercise, were collected to document stability of Hb values. Routine oximetry analysis (IL282 with bovine board, Instrumentation Laboratories, Inc., Lexington, MA) and HCT were performed on all samples.

Results

The effects of maximal incremental exercise on $\dot{V}o_2$, R, Hb, and HCT in control sheep and in sheep pretreated with epinephrine, propranolol, and phenoxybenzamine are shown in Table 1. Maximal exercise in control sheep resulted in a mean maximum $\dot{V}o_2$ of 47.6 ± 6.7 ml/min/kg with a range of 41.2 to 60.5 ml/min/kg. The R increased from 0.78 ± 0.16 to 1.13 ± 0.12. Maximal exercise caused a significant increase in Hb from 9.1 ± 0.4 to 13.1 ± 0.8 g/100 ml and a significant increase in HCT from 25.7 ± 1.1 to 36.5 ± 2.6%.

Figure 1 shows Hb during exercise for control sheep, sheep pretreated with epinephrine, and sheep pretreated with epinephrine without exercise. Exercise alone caused a rapid initial increase in Hb, a slower increase during the next 8 minutes, and a more rapid increase in the last 5 minutes. The response to epinephrine without exercise was characterized by a rapid increase in Hb followed by a decrease to baseline by 9 to 11 minutes after injection. The response to epinephrine and exercise was characterized by a rapid Hb increase prior to exercise, followed by an immediate decrease. After 4 to 7 minutes of exercise, Hb levels began to increase again, similar to elevations in Hb observed with exercise

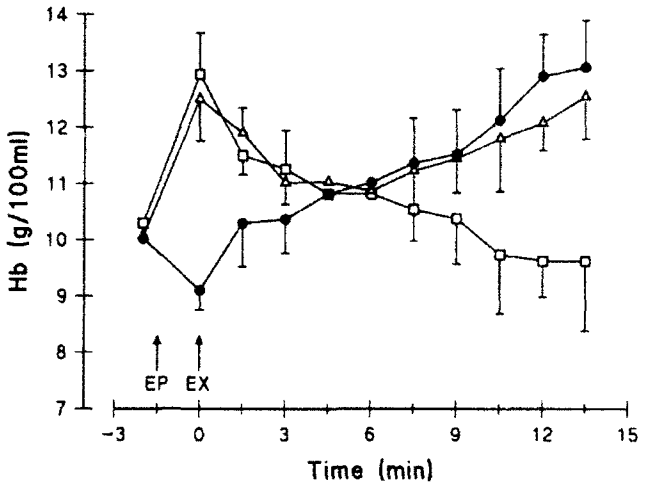

Figure 1. Venous (jugular) hemoglobin concentrations during maximal incremental exercise (●), during exercise after pretreatment with epinephrine (△) and after epinephrine without exercise (○). Values represent the mean ± standard deviation for six sheep in each group. EP = Epinephrine administration for epinephrine without exercise (○) and epinephrine with exercise (△) data. EX = begin exercise.

Table 1. Physiologic and hematologic data in response to maximal incremental exercise tests in control (untreated) sheep and sheep treated with epinephrine, propranolol and phenoxybenzamine

Variable	Control	Epinephrine	Propranolol	Phenoxybenzamine
Resting $\dot{V}o_2$	5.2 ± 3.5	6.9 ± 2.9	4.3 ± 3.2	4.0 ± 1.9
Maximum $\dot{V}o_2$	47.6 ± 6.7[a]	51.6 ± 8.7[a]	35.4 ± 15.3[ab]	40.8 ± 8.2[ab]
Resting R	0.78 ± 0.16	0.86 ± 0.18	0.81 ± 0.15	0.89 ± 0.06
Maximum R	1.13 ± 0.12[a]	1.14 ± 0.07[a]	1.04 ± 0.05[a]	1.15 ± 0.05[a]
Resting Hb	9.1 ± 0.4	10.1 ± 0.7	9.0 ± 0.7	8.9 ± 1.2
Maximum Hb	13.1 ± 0.8[a]	12.6 ± 0.8[a]	12.5 ± 0.5[a]	11.1 ± 0.7[ab]
Resting HCT	25.7 ± 1.1	28.6 ± 2.3	25.3 ± 2.5	24.8 ± 2.5
Maximum HCT	36.5 ± 2.6[a]	35.3 ± 0.8[a]	34.8 ± 1.8[a]	31.3 ± 0.8[ab]

Values are expressed as the mean ± standard deviation for six sheep in each group. Oxygen consumption ($\dot{V}o_2$, ml(STPD)/min/kg), gas exchange ratio (R), jugular hemoglobin (Hb) and hematocrit (HCT) at rest and at the end of maximal exercise are shown. [a]$P < 0.05$, compared to rest; [b]$P < 0.05$ compared to control sheep.

alone. Epinephrine did not increase mean maximum $\dot{V}o_2$ compared with controls (Table 1). Individual maximum $\dot{V}o_2$ data for control and epinephrine-treated sheep are shown in Figure 2.

Propranolol caused a significant decrease in maximum $\dot{V}o_2$, compared with controls (Table 1). Maximum $\dot{V}o_2$ was 47.6 ± 6.7 and 35.4 + 15.3 ml/min/kg for control and propranolol-treated sheep, respectively. Individual maximum $\dot{V}o_2$ for control and propranolol-treated sheep are shown in Figure 2. Figure 3 shows similar changes in Hb during exercise for control and propranolol-treated sheep. Figure 4 shows Hb concentrations during exercise for control and phenoxybenzamine-treated sheep. Alpha-blockade did not affect early Hb increases but ameliorated late exercise increases in Hb. Phenoxybenzamine caused a significant decrease in maximum $\dot{V}o_2$ compared with controls (47.6 ± 6.7 vs. 40.8 ± 8.2 ml/min/kg) (Table 1). Individual maximum $\dot{V}o_2$ for control and phenoxybenzamine-treated sheep are shown in Figure 2.

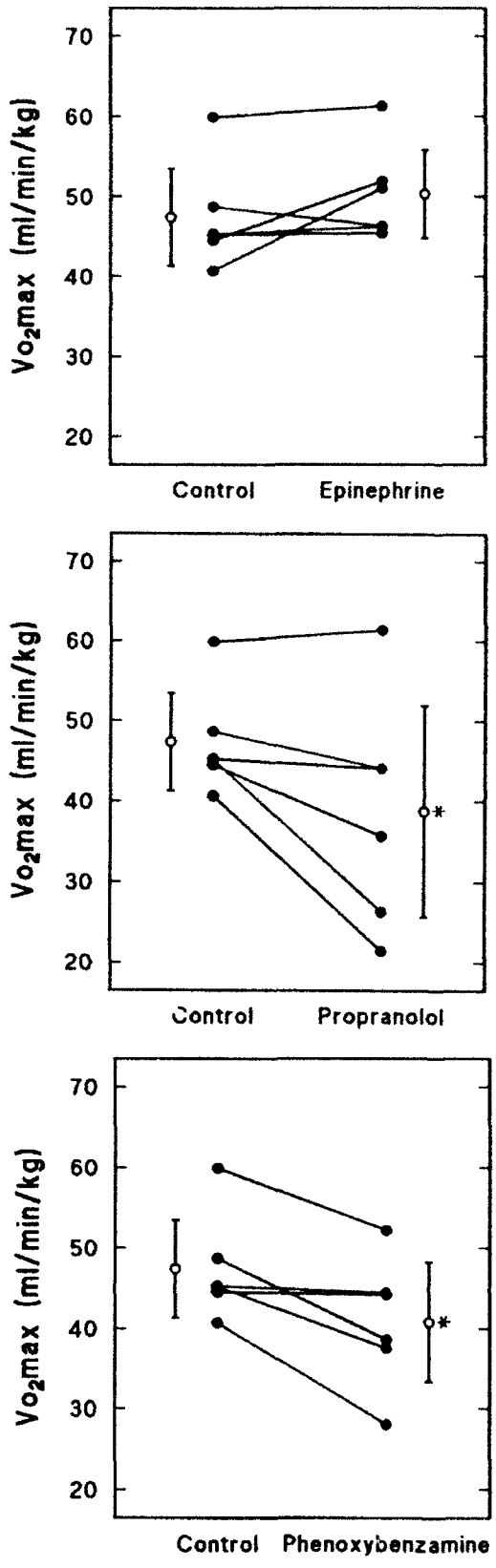

Figure 2. Individual and mean (± standard deviation) maximum $\dot{V}o_2$ for control exercise and after epinephrine, propranolol or phenoxybenzamine. * $P < 0.05$, compared with controls.

Discussion

Few studies of maximal exercise in sheep are available (14, 15). We recently reported changes in $\dot{V}O_2$ associated with three different incremental exercise protocols in sheep (15). In addition, endurance training caused increases in both maximum $\dot{V}O_2$ and treadmill time. In the currently reported study, significant increases in HCT were anticipated during maximal exercise in sheep, because sheep spleens have a large storage capacity (2) and because submaximal exercise has been shown to increase HCT (1). Exercise caused an increase in HCT and Hb of 42% and 44%, respectively. These increases were similar to increases that have been reported for dogs (16) and horses (17). Exercise studies of humans have shown a 5 to 10% increase in Hb due to plasma water changes during exercise. The results of previous studies in our laboratory have indicated less than 5% increase in Hb concentration in splenectomized sheep (18). Therefore, exercise-induced increases in Hb in sheep are primarily the result of splenic contraction, although changes in plasma water probably contribute a small part to this effect.

There was a significant increase in Hb after epinephrine administration to the sheep in our study. However, the effect was short-lived and most likely due to rapid splenic resequestration of red blood cells (2, 3). Moreover, when exercise followed epinephrine administration within 2 to 3 minutes, Hb continued to decrease until 4 to 6 minutes into the exercise protocol. At that time Hb values stabilized, and then subsequently increased, similar to control exercise (Figure 1). This effect clearly shows the effect of exogenous and then endogenous epinephrine on changing Hb concentration during exercise.

The observation that propranolol, a nonspecific ß-adrenergic blocking agent, decreased maximum $\dot{V}O_2$ during maximal incremental exercise was anticipated. However, this phenomenon in sheep has not been previously reported. This effect is thought to be primarily due to negative inotropic and chronotropic cardiac effects (19, 20), manifested in decreased cardiac output and heart rate (21). Propranolol did not alter normal Hb concentration increases observed during maximal exercise, suggesting that, at the dose tested, ß-adrenoceptors are not important in exercise-induced splenic contraction.

Pretreatment of sheep with phenoxybenzamine, a nonspecific α-adrenergic blocking agent, resulted in a smaller increase in Hb during exercise as compared with control exercise. Phenoxybenzamine did not inhibit early Hb increases, but it did inhibit late Hb increases as compared with controls (Figure 4). These data are consistent with studies of dogs (16) and horses (22), which also showed partial amelioration of Hb increases with α-blockade. One explanation for these data is that α-blockade was incomplete, and because we did not verify complete α-blockade, this possibility cannot be ruled out. However, assuming complete α-blockade, these data might suggest that splenic contraction during exercise is the result of two mechanisms. A first mechanism may be important in causing immediate Hb increase at the onset of exercise. These early exercise-induced Hb concentration increases may be caused by physical manipulation of the spleen, biochemical and/or neural mechanisms. A second mechanism, abated by α-blockade, is important in further Hb increases. Figure 4 suggests the importance of assuring an adequate resting Hb concentration. For example, if the first (-2 min) control value was accepted as resting Hb, a conclusion might be made that phenoxybenzamine almost totally blocked Hb increases. Allowing the animal to stand undisturbed for a few minutes permitted a better determination of resting Hb and thus was important for indicating that significant early increase in Hb occurred in the presence of α-adrenergic blockade.

Phenoxybenzamine-induced α-blockade reduced maximum $\dot{V}O_2$ by 14.3% (Table 1). This is consistent with the results of a study of dogs which indicated a decrease of similar magni-

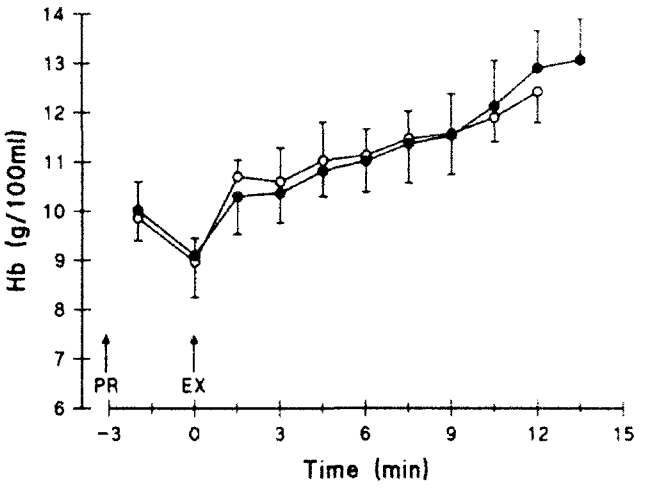

Figure 3. Venous (jugular) hemoglobin concentrations during maximal incremental exercise for control (●) and propranolol-treated (○) sheep. Values represent the mean ± standard deviation for six sheep in each group. PR = Propranolol administration 5 minutes prior to exercise. EX = begin exercise.

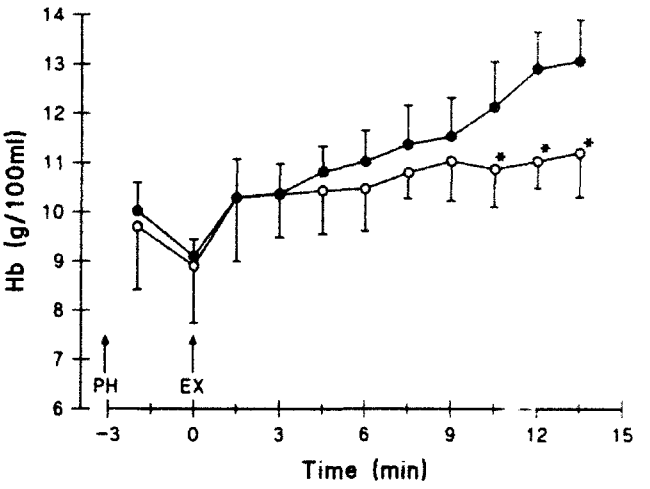

Figure 4. Venous (jugular) hemoglobin concentrations during maximal incremental exercise for control (●) and phenoxybenzamine-treated (○) sheep. Values represent the mean ± standard deviation for six sheep in each group. * $P < 0.05$ compared with controls. PH = Phenoxybenzamine administration 1 hour before exercise. EX = begin exercise.

tude after α-blockade (16). In that study, the authors proposed that the α-blockade effects of reduced cardiac output, arterial O_2 content and $(A\text{-}V)O_2$ difference, were responsible for the observed decrease in maximum $\dot{V}o_2$. A study of maximal exercise in humans showed negligible differences in maximum $\dot{V}o_2$, heart rate, cardiac output, and stroke volume between control and α-blocker-treated subjects (23). However, the results of that study showed lower mean arterial pressure and total peripheral resistance with α-blockade. The mechanism of decreased maximum $\dot{V}o_2$ in our study after α-blockade is unclear. Decreased Hb concentration may have been a contributing factor; however, it seems unlikely that the decrease in maximum $\dot{V}o_2$ can be totally explained by this mechanism. In fact, in another study, we failed to show a significant difference in maximum $\dot{V}o_2$ in normal sheep before and after splenectomy (18).

Data from our study provide further evidence that the spleens of exercising sheep are catecholamine-sensitive. Contraction of the spleen is stimulated by exogenous epinephrine or endogenous epinephrine which is released during exercise. Alpha-adrenergic blockers, but not ß-blockers, inhibit all but the initial increase in Hb during maximal exercise.

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Footnotes

The views of the authors do not reflect the position of the Walter Reed Army Institute of Research, the Walter Reed Army Medical Center, the Department of the Army, or the Department of Defense.

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